Welcome and introduction

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No set office hours – happy to meet anytime
Send me an email to make arrangements
Additional *optional* pharmacology texts

All on reserve at Woodward library

Overview of next 3+1 lectures

Part 1: Introduction
   What are drugs?

Part 2: Pharmacodynamics
   What do drugs do to the body?

Part 3: Pharmacokinetics
   What does the body do to drugs?

Part 4: Drug Dosing
   How do we design drug dosing regimens?
Part 1: Introduction to Pharmacology

Some definitions

What is Pharmacology?   pharmakon = drug
                        logos = the study of

∴ Pharmacology = the study of drugs
         → what they do and how they do it

≠ Pharmacy: the health profession that deals with the preparation and dispensing of (prescription) medications
“Drug” has many definitions

Webster’s Dictionary:
“a substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease”

More broadly:
“any substance that brings about a biological change or effect on the body”

Drugs come from many sources

Plants
Foxglove → Digoxin

Animals
Pregnant mare urine
↓
Premarin®
Drugs come from many sources

Minerals – Lithium

Synthetic – Sulfa drugs

Natural ≠ Safe!

Strict rules urged for energy drinks
Health Canada examining approach to high-caffeine products.

“Caffeine-loaded energy drinks have now crossed the line from beverages to drugs delivered as tasty syrups,” the Canadian Medical Association Journal says.

~Vancouver Sun, July 27, 2010
Vitamin drinks could cause harm
Some have too-high levels of vitamin A; Health Canada must act, experts warn

- Health Canada’s recommended daily intake of retinol for women is 700 mcg
- One 547mL Fuze Vitalize bottle contains 3000 mcg
- Increased risk of liver damage
- Potentially harmful for pregnant women – increased risk of birth defects

~Vancouver Sun, January 24, 2011

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One drug…many names

1. Chemical Name:
   Identifies the chemical elements and compounds that are found in the drug – most important to chemists, pharmacists and researchers who work with the drug at a chemical level.

2. Generic or Non-proprietary Name:
   The universally accepted name of a drug. It appears on all drug labels, resource guides and publications. Generic names often follow similar patterns for drugs of the same class or mechanism. (ex: lidocaine, procaine)

3. Brand or Trade or Proprietary Name:
   The copyrighted and trademarked name given by the drug company – restricts the use of the name.
One drug…many names

Chemical name: (±)-2-(p-isobutylphenyl) propionic acid
Generic name: Ibuprofen
Brand names: Advil®, Motrin®

Generic name: Loratadine
Brand name: Claritin®

Pharmacology has 2 arms

Pharmacodynamics
“what the drug does to the body”
• the study of the effect(s) of drugs on body processes

Pharmacokinetics
“what the body does to the drug”
• the study of the movement of drugs in the body (how it reaches and leaves its site of action and at what concentration)
The PK – PD relationship

Part 2: Pharmacodynamics
Simplification of drug action

Receptor  Drug – receptor complex  Biologic alteration  Pharmacologic effect(s)

What are receptors?

- Receptors are macromolecules that mediate a biological change following ligand (drug) binding

- Most receptors are proteins with:
  - 1° aa sequence
  - 2° regular sub-structures
  - 3° 3-D structure
  - sometimes 4° multi-protein complexes
**Where are receptors?**

- Receptors are located on the surface of or within cells

**The drug-receptor complex**

- Van der Waals forces, hydrogen and ionic bonds in the active (binding) site typically mediate formation of the drug-receptor complex → receptor affinity
An exception to the rule

- a few drugs work via non-receptor mechanisms, for example:

  **Antacids** - purely chemical basis via acid neutralization in the stomach

  **Osmotic diuretics** - promote urine excretion by altering water flow in the kidney independent of receptors

There are 4 main classes of receptors

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ligand-gated ion channels</td>
</tr>
<tr>
<td>B</td>
<td>G protein-coupled receptors</td>
</tr>
<tr>
<td>C</td>
<td>Enzyme-linked receptors</td>
</tr>
<tr>
<td>D</td>
<td>Intracellular receptors</td>
</tr>
</tbody>
</table>

**INTRACELLULAR EFFECTS**

- Change in membrane potential or [ion]
- Intracellular 2nd messengers
- Intracellular phosphorylation
- Altered transcription

**PHARMACOLOGIC EFFECTS**
**What binds to the receptors?**

- Most receptors have naturally occurring (endogenous) molecules that bind to them
- Exogenous (foreign) molecules can be designed to bind to the same receptor ⇒ rational drug design

*Example ~*

\[
\text{Endorphins (endogenous)} \quad \text{Morphine (exogenous)} \quad \text{Bind opiate receptors in brain} \quad \text{EUPHORIA}
\]

**Drugs can be agonists**

AGONISTS have:

1. **AFFINITY** for the receptor *(they bind to it)*
2. **INTRINSIC ACTIVITY** *(binding elicits a response)*

Agonists can be either

1. **Endogenous** *(ex: adrenalin)*
2. **Exogenous** *(ex: dobutamine)*

\[
\text{Drug} \quad \text{Receptor} \quad \text{Both } \uparrow \text{ rate} \quad \text{Effect}
\]
**Drugs can be antagonists**

ANTAGONISTS *(aka receptor blockers or inhibitors)*
1. have AFFINITY *(bind the receptor)*
2. LACK intrinsic activity *(no response)*

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**Antagonist example**

Claritin®: an antagonist that blocks histamine receptors ➔ allergy treatment
Pharmacologic effects – side effects

“A drug without side effects isn’t really a drug”

Side Effects/Adverse Effects

Mild, tolerable, subside on their own (ex: GI disturbances)

Potentially life-threatening & sustained (ex: seizures)

Risks vs benefits must be carefully weighed → Therapeutic Index

Side effect or not? A matter of perspective

“may cause drowsiness”

When taken for seasonal allergies

When taken as a sleep aid
The pharmacologic effect is related to dose

Drug dose-response curves

Therapeutic index: a measure of drug safety
**Therapeutic index: a measure of drug safety**

Narrow TI Drugs
- Digoxin
- Lithium
- Phenobarbital
- Vancomycin
- Warfarin

**Routes of drug administration**

[Diagram showing various routes of administration: Parenteral (IV, IM, SC), Sublingual, Inhalation, Oral, Transdermal patch, Rectal, Topical]
**Which route to use? 3 factors to consider**

1.  
   • size, water vs lipid solubility, pH stability

2.  
   • consciousness, ability to follow instructions, age, other medications

3.  
   • urgency of situation, local vs systemic effects

**Enteral administration (systemic effect)**

• involves the gastro-intestinal (GI) tract
  ▪ oral (po) – most common
  ▪ sublingual (sl)
  ▪ rectal (pr)

*Advantages:* convenient, inexpensive, safe

*Disadvantages:* possible 1st-pass metabolism, pH stability, variable absorption
**Parenteral administration (systemic effect)**

- does not involve the GI tract (usually injections)
  - intravenous (iv)
  - subcutaneous (sc, subQ)
  - intramuscular (im)

  **Advantages:** immediate – no absorption (iv), avoids stability concerns, unconscious OK

  **Disadvantages:** discomfort, potential for infection

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**Other routes**

**Inhalational (systemic or local effect)**
- metered dose inhalers, general anesthetics, nasal decongestants

**Topical (local effect)**
- cream, ointment, drops

**Transdermal (systemic effect)**
- patch
The drug is now in the body...what next?

“Pharmacokinetics”

Part 3: Pharmacokinetics
Claritin monograph

What words or phrases in the drug monograph are unfamiliar to you?

Source: Compendium of Pharmaceuticals and Specialties (CPS)

Claritin monograph

- pharmacokinetics
- elimination
- half-life
- $C_{\text{max}}$
- $T_{\text{max}}$
- steady state
- bioavailability
- active metabolite
- unchanged drug
- conjugated drug
- clearance
The PK – PD relationship

**Pharmacokinetics**

**Pharmacodynamics**

Dosage Regimen
How much? How often? How long? What form?

[DRUG] - Plasma

[DRUG] - Receptors at Target Site

Pharmacological Effects

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**Pharmacokinetics – the ADME processes**

**A**
gets drug into the blood

**D**
where it goes in the body

**M**
what happens to it

**E**
how it gets out
Absorption

- The movement of drug from site of administration into the blood → occurs by *passive diffusion*

**Influencing Factors:**

- concentration gradient (hi → low)
- drug size (must be less than 1 kDa)
- lipid solubility / pH

_Membrane permeability – effect of lipid solubility_

- Only uncharged, hydrophobic drugs can passively diffuse across lipid bilayers (membranes)
**Membrane permeability – effect of pH**

- Most drugs are weak acids or weak bases – exist in equilibrium between protonated & unprotonated, charged & uncharged species

  weak acid drug \[ \text{HA} \rightleftharpoons \text{H}^+ + \text{A}^- \]

  weak base drug \[ \text{B} + \text{H}^+ \rightleftharpoons \text{BH}^+ \]

- pH of environment and pKa of drug dictate which of the two forms predominates

**Weak acid and weak base drugs**

Total weak acid drug = \[ \text{HA} + \text{A}^- = \]

\[
\begin{array}{ll}
99\% & 1\% \\
50\% & 50\% \\
12\% & 88\%
\end{array}
\]

Total weak base drug = \[ \text{BH}^+ + \text{B} = \]

\[
\begin{array}{ll}
99\% & 1\% \\
50\% & 50\% \\
12\% & 88\%
\end{array}
\]
Membrane permeability – effect of pH

- Only the uncharged (unionized) species will cross the membrane (*ie be absorbed*)

Predicting absorption/diffusion

- We can use the Henderson-Hasselbalch equation to predict the extent to which this will occur

\[
\text{pH} = \text{pKa} + \log \left( \frac{\text{unprotonated form}}{\text{protonated form}} \right)
\]
Practice calculation 1

Piroxicam is a weak acid (pKa=1.8) that is used to relieve arthritic pain. How much of it will diffuse across the gastric mucosal barrier and into the blood (plasma) when taken orally?

Practice calculation 2

The first dose provides temporary pain relief but also causes stomach upset. The person decides to take a 'Tums' with her next dose.

After this her stomach is no longer upset, but now her pain won't go away. Why?

(Tums raises the stomach pH by 2 units)
**Bioavailability (fraction absorbed, F)**

- the fraction of drug that reaches systemic circulation unchanged

\[
F = \frac{\text{amount of drug in systemic circulation}}{\text{amount of drug administered}}
\]

What can you do to ensure a drug is 100% bioavailable (F=1)?

- non-iv dosage recommendations take fractional absorption into account
- useful for comparing routes of administration

**Question…**

When comparing the iv vs po routes of administration, which would require a larger dose of the same drug in order to achieve the same effect? Why?
**How does the drug know where to go?**

drug circulates throughout body in the blood
\[\downarrow\]
encounters receptors for which it has affinity
\[\downarrow\]
binds
\[\downarrow\]
pharmacological response

**Distribution**

➤ The process by which drug reversibly leaves the bloodstream
  • drug moves between body compartments
  • drug reaches the site of action (receptors)

Influencing Factors:

- conc. gradient
- drug size
- lipid solubility / pH
- blood flow
- protein binding
Distribution – effect of blood flow

- Drug is delivered to tissues in relation to perfusion

Distribution – effect of protein binding

- Drugs reversibly bind plasma (blood) proteins
  (protein + drug \( \rightleftharpoons \) drug-protein complex)

- Proteins are large – sequester (trap) drug in blood
  \( \therefore \) drug can’t distribute to target receptors
  \( \therefore \) protein bound drug is pharmacologically inactive

- Concentration of free drug in blood ↓
  \( \therefore \) less pharmacologically active drug

Most drug dosing regimens take protein binding into account
BUT there are situations where protein profiles are altered
(pregnancy; disease) and dosing needs to be adjusted
**Effect of protein binding**

<table>
<thead>
<tr>
<th>Weakly protein bound drug</th>
<th>Highly protein bound drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Diagram of weakly bound drug" /></td>
<td><img src="image2.png" alt="Diagram of highly bound drug" /></td>
</tr>
</tbody>
</table>

**Volume of distribution (Vd)**

- **Administration:** dose or amount \((mg, \mu g)\)
- **Plasma analysis:** concentration \((mg/L, \mu g/mL)\)

\[
\text{Concentration} = \frac{\text{dose}}{V_d}
\]

*Which volume do we use?*
**Volume of distribution (Vd)**

There are several physiological fluid compartments into which hydrophilic drugs can distribute.

Total body water (TBW) = 70kg x 1L/kg x 0.6 = 42L

- hypothetical PK man
- density of water
- body ~60% water

**Examples:**

- Heparin = 3L → Plasma
- Gentamicin = 18L → ECF
- Ethanol = 38L → TBW

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**A clinical example**

A 30mg dose of the antidepressant Nortriptyline is administered to a patient iv and a plasma concentration of 25μg/L is subsequently measured.

What is the volume of distribution of this drug?
What is volume of distribution?

- NOT a real, physiological volume but rather a proportionality constant that relates the amount of drug in the body to its concentration in the blood

- The magnitude of Vd indicates the extent of drug distribution in the body, but not the location

Large Vd (>42 L): drug distributes outside blood and body fluids into tissues

Small Vd (≤42 L): drug has limited distribution, typically restricted to blood or physiological fluids
**Distribution notes in pregnancy**

1. Plasma protein levels are **DECREASED** in pregnancy ~ **what affect will this have on drug activity?**

2. The placenta is **NOT a barrier to drug transport** – small (<500 Da) MW, lipophilic, un-ionized drugs passively diffuse

3. **P-glycoprotein (Pgp)**
   drug transporter pumps drugs from fetal to maternal side

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**Metabolism**

- the irreversible biotransformation of drug
  - makes it **more polar** to ↑ renal (urinary) excretion

Occurs primarily in the liver via 2 (usually sequential) enzyme-catalyzed processes:

- Phase I **oxidation/reduction/hydrolysis**
- Phase II **conjugation**
**Phase I: cytochrome P450 enzymes**

A superfamily of related enzymes that add on or uncover small polar groups (–OH, –NH₂, –COOH) to \( \uparrow \) water solubility

### P450 Enzymes

<table>
<thead>
<tr>
<th>P450 Enzymes</th>
<th>CYP2D6</th>
<th>CYP1A2</th>
<th>CYP2C19</th>
<th>CYP2C9</th>
<th>CYP3A4/5</th>
<th>CYP2A6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19%</td>
<td>11%</td>
<td>8%</td>
<td>16%</td>
<td>36%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**P450 enzyme induction and inhibition**

- some P450 enzymes can be induced or inhibited by other drugs, foods, pregnancy or disease

**Induction:** \( \uparrow \) metabolic activity of enzymes

\[ \therefore \text{[Drug]} \quad (\text{ex: alcohol}) \]

**Inhibition:** \( \downarrow \) metabolic activity of enzymes

\[ \therefore \text{[Drug]} \quad (\text{ex: grapefruit juice}) \]

- Primary cause of drug interactions
- Requires drug dosing to be increased or decreased
- P540 enzyme profile changes in pregnancy:
  - \( \uparrow \) in CYP 2D6, 3A4 and 2C9
  - \( \downarrow \) in CYP 1A2 and 2C19
Practice problem

Relative to a non-pregnant woman, how would drug dosing need to be altered (↑ or ↓) for the following drugs in pregnancy:

1. Erythromycin (metabolized by Cyp3A4)
2. Omeprazole (metabolized by Cyp2C19)
3. Paroxetine (metabolized by Cyp2D6)
4. Ibuprofen (metabolized by Cyp2C9)
5. Caffeine (metabolized by Cyp1A2)

Phase II: conjugative enzymes

Mediated by various non-P450 liver enzymes
- covalently add large, polar, endogenous molecules to Phase I metabolite
- ensures that metabolite is ready for excretion

(glucuronide, glutathione, sulfate, acetate, amino acids etc)
**Drug metabolism**

- usually inactivates the drug
- is required to activate prodrugs

Metabolite + Receptor ≠ MR complex

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**Drug metabolism**

- may be harmful if the metabolite(s) are toxic

Tylenol® = Acetaminophen

Phase I CYP2E1 Induced by alcohol
**First pass metabolism**

Most drugs absorbed from the GI tract are delivered to the liver before reaching the systemic circulation.

∴ oral doses > iv doses to account for loss due to metabolism

**Drug metabolism in the gut**

Some drugs undergo significant metabolism by bacterial enzymes in the gut (*ex: digoxin*)

What effect might a course of antibiotic therapy have in a person taking digoxin?
**Metabolism notes in pregnancy**

1. P450 enzymes are altered in pregnancy (see previous)

2. The placenta is capable of metabolizing drugs, but this is of little relevance to the mother (*i.e.* it does not significantly impact the maternal drug concentration)

3. However, placental metabolism can protect the fetus from drug exposure (some P450 and conjugation)

4. The fetal liver is capable of metabolizing drugs by *oxidation* reactions only (all other enzymes are not yet developed)

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**Excretion – kidney (renal excretion)**

- The irreversible loss of drug from the body

1. **Passive Glomerular Filtration**
   - diffusion of small drugs <20kDa

2. **Active Tubular Secretion**
   - transport systems for large drugs
   - *Pgp acts here*

3. **Passive Tubular Reabsorption**
   - concentration gradient may drive uncharged drug back into blood
   - *urine pH is key*
Absorbed or Excreted?

Weak acid: \[ HA \rightleftharpoons H^+ + A^- \]

Weak base: \[ B + H^+ \rightarrow BH^+ \]

Changing urine pH to treat an overdose

- increasing urine pH shifts equilibrium to promote excretion of weak acid drugs (*ex: aspirin*)
  - iv sodium bicarbonate raises pH from 6-8

\[ HA \rightleftharpoons H^+ + A^- \]

Ionized form is water soluble \[ : \] excreted in urine

*Remember: \( \uparrow \) pH = \( \downarrow \) \([H^+]\)
Changing urine pH to treat an overdose

How would you modify the urine pH to treat an overdose of a weak base drug?

\[ \text{B} + \text{H}^+ \rightleftharpoons \text{BH}^+ \]

Excretion – bile/feces (aka biliary excretion)

- Drugs and/or metabolites actively secreted into biliary tract – delivered to duodenum via common bile duct *Pgp acts here

- Carrier-mediated process ∴ protein binding & ionization are not limiting factors
Excretion – breast milk

1. Breast milk is a relatively minor route of drug excretion from mother’s perspective

2. Potentially significant for nursing baby

3. Breastmilk pH < plasma (7.2 vs 7.4) → what group of drugs will concentrate (be trapped) in breastmilk – weak acids or bases?

4. Drugs of concern: CNS depressants, sedatives, anticancer drugs

Summary
## Claritin® Schering

**Loratadine**

**Histamine H1-Receptor Antagonist**

Pharmacology: Loratadine is a long-acting tri cyclic antihistamine with selective peripheral H1-receptor antagonistic activity. It exhibits a dose-related inhibition of the histamine-induced skin wheal and erythema responses in humans which is rapid in onset, is apparent at 2 hours and persists throughout the 24-hour observation period. Single oral doses up to 160 mg and repeat daily doses of 40 mg for up to 13 weeks were well tolerated with the incidence of sedation and dry mouth being no different from placebo.

Pharmacokinetics: α-C-Loratadine is rapidly absorbed reaching Cmax values (4.7, 10.8 and 28.1 ng/mL) at 1.5, 1.0 and 1.3 hours for the 10, 20 and 40 mg dose, respectively. The loratadine elimination half-life (t1/2) ranged from 7.8 to 11 hours. Desacetoxyloratadine, the major active metabolite, reached Cmax values (4.0, 9.9 and 16.0 ng/mL) at 3.7, 1.5 and 2.0 hours after a dose of 10, 20 and 40 mg, respectively. Its t1/2 β ranged from 17 to 24 hours. The accumulation indices, calculated by Cmax and the area under the curve (AUC), did not change after the fifth day, indicating little or no accumulation of either loratadine or its metabolite after a multiple once per day dosage regimen. The t1/2 β at steady-state levels for loratadine and its metabolite were 14.4 and 18.7 hours, respectively, similar to that reported following a single oral dose.

The confidence intervals for Cmax and AUC of α-C-Loratadine are within the 80 to 125% range indicating that the Claritin® or Dose-Dependent Tablets were bioequivalent with respect to the active metabolite desacetoxyloratadine.

After administration of a single 10 mg dose of loratadine as either the Claritin® or Dose-Dependent Tablets, a conventional tablet, or the syrup formulation (1mg/ml), peak plasma concentrations of loratadine and its metabolite were achieved at approximately 1 and 2 hours, respectively; mean elimination half-life of the active metabolite ranged between 19 and 21 hours. See Tables I and II.

Since loratadine is extensively metabolized there was a high inter-subject variability in the plasma drug concentrations. Hence, the percent coefficient of variation (CV) of the pharmacokinetic parameters was large.

Following administration of 10 mg of loratadine once daily for 10 days as either a Claritin® or Dose-Dependent Tablets or a conventional tablet, plasma concentrations of loratadine and its active metabolite were at steady state by day 5 with both formulations. Mean peak plasma concentrations (Tmax) of loratadine and its metabolite in both formulations were attained at 1.3 hours; peak to trough fluctuations observed for the Claritin® and conventional tablet were similar with respect to loratadine and its metabolite. Mean elimination half-life of the active metabolite was 20 hours for both formulations. See Table III.

### Table I—Claritin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Claritin® Rapid Dose Dissolve 10 mg Tablet</th>
<th>Mean (CV%)</th>
<th>Claritin® 10 mg Tablet (Conventional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadine</td>
<td>DCL1</td>
<td>Loratadine</td>
<td>DCL2</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>2.56 (83)</td>
<td>3.72 (63)</td>
<td>2.11 (90)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.14 (72)</td>
<td>1.97 (129)</td>
<td>1.00 (34)</td>
</tr>
<tr>
<td>AUC0-24 (ng·h/mL)</td>
<td>5.14 (100)</td>
<td>49.1 (50)</td>
<td>4.64 (106)</td>
</tr>
</tbody>
</table>

*Coefficient of variation.

### Table II—Claritin

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<tr>
<td>Cmax (ng/mL)</td>
<td>2.65 (193)</td>
<td>3.46 (44)</td>
<td>3.62 (150)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.00 (30)</td>
<td>1.42 (38)</td>
<td>0.98 (44)</td>
</tr>
<tr>
<td>AUC0-24 (ng·h/mL)</td>
<td>0.53 (221)</td>
<td>40.8 (25)</td>
<td>10.1 (147)</td>
</tr>
</tbody>
</table>

*Coefficient of variation.

### Table III—Claritin

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<tr>
<th>Parameter</th>
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<td>Cmax (ng/mL)</td>
<td>3.79 (83)</td>
<td>3.35 (75)</td>
<td>4.04 (80)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>12.0 (78)</td>
<td>11.2 (75)</td>
<td>12.7 (71)</td>
</tr>
</tbody>
</table>

*CV: Coefficient of variation.

### Table IV—Claritin

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Claritin Tablets, 10 mg Daily vs Placebo and Comparatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Adults Reporting Frequently Occurring (&gt;2% of Loratadine-treated Patients)</td>
<td>Adverse Experiences in Adults Possibly or Probably Related to Treatment: Claritin® Tablets and Comparatives</td>
</tr>
</tbody>
</table>

Number (%) of Patients Reporting Frequently Occurring (>2% of Loratadine-treated Patients) Adverse Experiences in Adults Possibly or Probably Related to Treatment: Claritin® Tablets and Comparatives

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Claritin® Rapid Dose Dissolve Tablets vs Claritin® Conventional Tablets vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients Reporting Frequent Occurring (&gt;2% of Claritin® Tablets-treated Patients)</td>
<td>Adverse Experiences Possibly or Probably Related to Treatment in Seasonal Allergic Rhinitis Studies</td>
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### Table V—Claritin

<table>
<thead>
<tr>
<th>Adverse Experience</th>
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Number (%) of Patients Reporting Frequently Occurring (>2% of Claritin® Tablets-treated Patients) Adverse Experiences Possibly or Probably Related to Treatment in Seasonal Allergic Rhinitis Studies

<table>
<thead>
<tr>
<th>Number (%) of Patients</th>
<th>Claritin® Rapid Dose Dissolve Tablets vs Placebo</th>
</tr>
</thead>
</table>
Weak acid dissociation eqn: \[ HA = H^+ + A^- \]

Want to solve for the unionized form \( \Rightarrow \) absorbable

\[ pH = pK_a + \log \frac{A^-}{HA} \]

\[ 1.0 = 1.8 + \log \frac{A^-}{HA} \]

\[ -0.8 = \log \frac{A^-}{HA} \]

antilog(-0.8) = \( 10^{-0.8} \) = 0.158 = \( \frac{A^-}{HA} \)

Which is the same as

\[ \frac{0.158}{1} = \frac{A^-}{HA} \]

\% HA = \( \frac{HA}{A^- + HA} \times 100 = \frac{1}{(0.158 + 1)} \times 100 = 86\% \)